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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/933,717	08/22/2001	Masahiro Imoto	1830/50325	6281

7590 12/03/2004

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EXAMINER	
COLEMAN, BRENDA LIBBY	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 12/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/933,717	IMOTO ET AL.	
	Examiner	Art Unit	
	Brenda Coleman	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,8,10,13 and 17-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,8,10,13 and 17-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/2001, 7/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Claims 1, 4, 8, 10, 13 and 17-29 are pending in the application.

This action is in response to applicant's amendment filed September 14, 2004. Claims 1, 4, 8, 10, 13, 17 and 18 have been amended and claims 19-29 are newly added.

Change of Examiner

Note the change of Examiner in the present application.

Response to Amendment

Applicant's arguments filed September 14, 2004 have been fully considered with the following effect:

1. The applicant's amendments and arguments are sufficient to overcome the 35 USC § 132, objection labeled paragraph 1 of the last office action, which is hereby **withdrawn**.

2. The applicant's amendments and arguments are sufficient to overcome the 35 USC § 112, second paragraph rejections of the last office action, which are hereby **withdrawn**.

In view of the amendment dated January 26, 2004, the following new grounds of rejection apply:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 4, 8, 10, 13 and 17-29 and are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQZd 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The nature of the invention in the instant case has claims, which embrace substituted imidazoles and pyrimidines.

HOW TO USE: Claims 1, 4, 8, 10, 13 and 17-29 are to compounds, compositions and method of use of the compounds of formula (I) where the method is a method of treating a disease, which is responsive to the activity of nicotinic Ach

receptors. Any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the effectiveness of the claimed compounds. However, the specification provides no definitive evidence to correlate any one disorder selected from those disclosed in the specification with the instantly disclosed imidazole and pyrimidine derivatives. No screening protocols are ever described. Thus, no evidence of in vitro effectiveness is seen in the specification for one of the instantly claimed imidazole and pyrimidine derivatives. In general, pharmacological activity is a very unpredictable area. In cases involving physiological activity "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Since this case involves unpredictable in-vivo physiological activities, the scope of the enablement given in the disclosure presented here was found to be low. The specification does not have working examples on the use of the substituted imidazoles and pyrimidines. The absence of working examples is one of the factors to be considered in deciding whether the practice of an invention would involve undue experimentation. There must be evidence to justify the contention that the claimed compounds can be useful in the treatment of cerebral circulation diseases, neurodegenerative disease dementia, motor ataxia, neuropathy, mental diseases, improving the cerebral metabolism, neurotransmission functional disorder, etc.

4. Claims 1, 4, 8 and 19-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The definition of the substituents on the phenyl group, i.e. nitro and cyano in the definition of R^8 and R^9 is not described in the specification with respect to the genus.

Applicant is required to cancel the new matter in the reply to this Office action.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claims 1, 4, 8, 10, 13 and 17-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claim 18 recites the limitation "4,5-dimethyl" in the third species. There is insufficient antecedent basis for this limitation in the claim.

b) Claim 18 recites the limitation "4-methyl" in the fifth species. There is insufficient antecedent basis for this limitation in the claim.

c) Claim 18 is vague and indefinite in that fails to end in a period indicating the end of the claim.

d) Claims 1, 4, 8, 10, 13 and 17-29 are vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the disorders capable of being treated by modulating the activity of acetylcholine receptors. Determining whether a given disease responds or does not responds to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties in

vivo, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus *iv* or in a time release *po* formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active in vivo, simply is not potent enough or produces such low concentrations in the blood that it is not an

effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of which are inhibitors in vitro, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property, which the second drug is capable. It is common for a drug, particularly in analgesics, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to affect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy, which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1, 4, 10 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0 268 915. EP 0 268 915 teaches the compounds of the instant invention where A is 1-chloro-thiazol-5-yl or 6-chloro-pyridin-3-yl and -Y-X- forms –CH=CH-N= or -CH=CH-CH=N-. See page 33.

7. Claims 1, 4, 8 and 19-22 are rejected under 35 U.S.C. 102(b) as being anticipated by CHAO et al., Pesticide Biochemistry and Physiology. CHAO teaches the compounds, compositions and method of use of the compounds of the instant invention where A is 6-chloro-pyridin-3-yl and -Y-X- forms –CH=CH-N=. See page 79, number 4.

8. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by BROWN et al., J. Chem. Soc. BROWN teaches the compounds of the instant invention where A is phenyl or 4-nitrophenyl and -Y-X- forms -CH=CH-CH=N-. See page 908.

9. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by COX et al., J. Agric. Food Chem. COX teaches the compounds of the instant invention where A is 6-chloro-pyridin-3-yl and -Y-X- forms -CH=CH-N=. See page 1469.

10. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by JANSSENS et al., U.S. Patent No. 6,169,097. JANSSENS teaches the compounds of the instant invention where A is 4-fluorophenyl and -Y-X- forms -CH=CH-N=. See column 19, Example A8.

Conclusion

11. Applicants' attention is directed to U.S. Patent No. 6,303,638, which while not competent as a reference against the instant claims in view of the applicants' filing of a certified translation of their priority document, claims subject matter that is similar and/or identical to that claimed herein. Two patents cannot issue on the same subject matter, unless applicants can demonstrate that the claims are patentably distinct from the claims of this US patent, the only way to overcome this patent is by way of Interference proceedings or removal of the conflicting subject matter. See MPEP 2306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Coleman whose telephone number is 571-272-0665. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brenda Coleman

Brenda Coleman
Primary Examiner Art Unit 1624
November 28, 2004